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ORIGINAL REPORT

Multicenter Phase II Trial of Sunitinib in the Treatment of Nongastrointestinal Stromal Tumor Sarcomas

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ABSTRACT

Purpose
To evaluate the potential benefit of continuous daily dosing sunitinib in patients with advanced nongastrointestinal stromal tumor (GIST) sarcomas.

Patients and Methods
A total of 53 patients with advanced non-GIST soft tissue sarcomas received sunitinib 37.5 mg daily. Primary end point was Response Evaluation Criteria in Solid Tumors defined response. Secondary end points were stable disease at 16 and 24 weeks. [^{18}F]-fluorodeoxyglucose positron emission tomography was performed on a subset of 24 patients at baseline and after 10 to 14 days of therapy.

Results
Forty-eight patients were eligible for response. One patient (desmoplastic round cell tumor [DSRCT]) achieved a confirmed partial response (PR) and remained on study for 56 weeks. Ten patients (20%) achieved stable disease for at least 16 weeks. Metabolic PR was seen in 10 (47%) of 21 of patients. Metabolic stable disease was seen in 11 (52%) of 21. There were no unexpected toxicities observed.

Conclusion
Sunitinib demonstrated notable evidence of metabolic response in several patients with non-GIST sarcoma. The relevance of disease control observed in subtypes with an indolent natural history is unknown, however, the durable disease control observed in DSRCT, solitary fibrous tumor, and giant cell tumor of bone suggests that future evaluation of sunitinib in these subtypes may be warranted.

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INTRODUCTION

Sarcomas are uncommon malignant mesenchymal neoplasms, comprising approximately 1% of all malignancies, and include more than 50 histologic subtypes of soft tissue sarcoma.[1] For early-stage localized soft tissue sarcomas, surgery, with or without radiotherapy, is the primary treatment. More than half of these patients, however, develop advanced disease, and prognosis for patients with advanced disease is poor.[2]

Given the need for improved therapies, investigations into novel treatments for advanced soft tissue sarcoma are ongoing. Recent efforts have focused on therapies specifically targeting tyrosine kinase signaling pathways involved in the growth and survival of malignant cells. The tyrosine kinase inhibitor imatinib has revolutionized the treatment of gastrointestinal stromal tumors (GIST) through inhibition of the activated tyrosine kinase, KIT.[3] Imatinib has also demonstrated activity in other sarcoma subtypes: dermatofibrosarcoma protuberans (DFSP) and aggressive fibromatosis (also called desmoid tumor), likely via inhibition of aberrant expression of platelet-derived growth factor receptor beta (PDGFR-β).[4-6]

Sunitinib malate is a multitargeted tyrosine kinase inhibitor with activity against vascular endothelial growth factor receptors (VEGFRs) 1, 2, 3, PDGFR-α, PDGFR-β, KIT, FLT3, RET, and CSF-1.[7] This broad range of activity may confer both antiangiogenic effects and direct antitumor effects depending on the tumor subtype. Sunitinib, when administered as 50 mg daily for 4 weeks followed by a 2-week rest cycle, has demonstrated clear efficacy in metastatic renal cell carcinoma and imatinib-resistant GIST, earning US Food and Drug Administration approval for these indications.[8,9] Recently, an alternative dosing strategy of daily administration of sunitinib 37.5 mg daily (continuous daily dosing),

with no planned breaks, has demonstrated comparable benefit in GIST without increase in toxicity.[10] Previous studies of sunitinib as a single agent in advanced GIST have shown early metabolic response using [^{18}F]-fluorodeoxyglucose positron emission tomography (FDG-PET).[11] This study was designed to evaluate the potential benefit of continuous daily dosing of sunitinib in non-GIST sarcomas.

PATIENTS AND METHODS

Patients

Adults age 18 or older with metastatic and/or locally advanced incurable connective tissue neoplasms other than GISTs were eligible. Additional key inclusion criteria were: history of fewer than three prior cytotoxic therapies for advanced disease; Response Evaluation Criteria in Solid Tumors (RECIST) measurable disease; Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2; adequate hematologic, hepatic, and renal function.

Key exclusion criteria were: clinically significant thyroid abnormality; evidence of a bleeding diathesis or the use of therapeutic anticoagulation; major surgery or National Cancer Institute Common Toxicity Criteria Adverse Events (NCI CTCAE) grade 3 or higher hemorrhage within 4 weeks of starting study treatment; clinically significant cardiovascular disease or uncontrolled hypertension; active brain metastasis; and concurrent administration of drugs known to alter CYP3A4 metabolism. Prior treatment with sunitinib or concurrent treatment with other investigational agents was prohibited.

The study was approved by the institutional review boards of the participating institutions and was registered with clinicaltrials.gov. Written informed consent was obtained from all patients before study participation. The study was conducted according to institutional and federal guidelines.

Study Design

This was an open-label, multicenter, phase II study of continuous dosing of sunitinib at 37.5 mg daily in patients with advanced or metastatic non-GIST sarcoma. Patients were enrolled to one of three arms in the study. Group A included vascular connective tissue neoplasms, leiomyosarcoma, dermatofibrosarcoma protuberans (DFSP), and desmoid tumors, a group of tumors that have shown responses to kinase-targeted agents in prior research. Group B included high grade undifferentiated pleomorphic sarcoma and other non-GIST connective tissue tumors, a group that has not clearly shown response to kinase-targeted agents. After initial patient enrollment, the study was amended to include group C which was comprised of chordomas only.

The primary end point of the study was RECIST-defined response for each stratum of patients. Secondary end points included progression-free rate at 16 weeks and 24 weeks of therapy, overall survival, and evaluation of metabolic response based on changes in tumor glycolytic activity as defined by positron emission tomography with FDG-PET and European Organisation for Research and Treatment of Cancer (EORTC) criteria[13] before and after 2 weeks of therapy.

Treatment

Patients self-administered sunitinib 37.5 mg orally once daily, without planned treatment breaks. Dose modifications were made for toxicities graded according to the Cancer Therapy Evaluation program, NCI CTCAE, version 3.0. Grade 3 and 4 toxicities except for hypertension were treated by holding sunitinib until the toxicity was $\leq$ grade 1. Recurrence of grade 3 toxicity necessitated dose reduction. Grade 2 or higher hypertension was treated with antihypertensive medications until the blood pressure was grade 1 or lower without discontinuation of sunitinib. If after 2 weeks of antihypertensive therapy, patients remained with grade 2 or higher hypertension, they were instructed to hold sunitinib until resolution to grade 1 or lower, and then to reduce the dose to 25 mg. Resolution of all adverse events within 4 weeks was required for continuation on study.

Assessments

Patients were evaluated approximately every 28 days. Tumor imaging with computed tomography (CT) scans, and assessment of left ventricular function was performed at baseline and every 8 weeks while the patient remained on study. Anatomic response assessments were performed locally at each site based on the longest diameter tumor measurements according to RECIST.[12] Treatment decisions were based on clinical information and CT response assessments only. A subset of 24 patients underwent FDG-PET/CT scans at baseline and again after 10 to 14 days on therapy. For each patient, up to five target lesions were identified on the baseline FDG-PET images based on hypermetabolic uptake. The maximum standardized uptake value (SUVmax) within each tumor region of interest was used as the comparative metric for metabolic response. Percentage change in the summed SUVmax of target lesions for each patient was calculated at follow-up compared to baseline. Metabolic response was assessed using EORTC thresholds for percent SUVmax change (PR $< -25\% \leq$ SD $\leq +25\% <$ PD), where PR is partial response, SD is stable disease, and PD is progressive disease.[13]

Statistical Methods

A Simon two-stage design was used for groups A and B. A 5% response rate was considered not promising, and a 20% response rate was considered promising. The type I error rate was set at 0.05 and the type II error was set at 0.10. For each of groups A and B, 21 patients eligible and assessable for response were planned for accrual. If one or fewer responses (defined as either a complete or partial response by RECIST) were observed, no further accrual

Table 1. Baseline Patient Characteristics

Characteristic	No.	%
Total eligible patients	51	
Total patients assessable for response*	48	
Median age, years	52	
Range	18-79	
Sex		
Male	25	49
Female	26	51
ECOG performance status		
0	37	73
1	13	25
2	1	2
No. of prior systemic therapies	2	
Range	0-3	
Prior anthracycline therapy	20	42
Histology of those assessable for response		
Group A†	18	
Leiomyosarcoma	11	23
Solitary fibrous tumor/hemangiopericytoma	3	6
Angiosarcoma	2	4
Desmoid	1	2
Intimal sarcoma	1	2
Group B	21	
Sarcoma NOS/malignant fibrous histiocytoma	5	10
Synovial sarcoma	4	8
Carcinosarcoma	3	6
Desmoplastic small round cell	3	6
Liposarcoma	2	4
Alveolar soft parts sarcoma	1	2
Clear cell sarcoma	1	2
Extraskeletal myxoid chondrosarcoma	1	2
Giant cell tumor of bone	1	2
Group C	9	
Chordoma	9	19

Abbreviations: ECOG, Eastern Cooperative Oncology Group; NOS, not otherwise specified.

*Two patients withdrew consent prior to restaging, one patient had an early severe adverse event prior to restaging.

†Three patients with chordomas were initially included in group A prior to the creation of group C. This accounts for the total of only 18 patients enrolled in group A.

Table 2. Responses by Response Evaluation Criteria in Solid Tumors

Group	No. Assessable for Response	PR + CR		SD			
				At 16 Weeks		At 24 Weeks	
		No.	%	No.	%	No.	%
A	18	0		2	11	2	11
B	21	1	4	4	19	3	14
C	9	0		4	44	2	22
Total	48	1	2	10	20	6	12

Abbreviations: PR, partial response; CR, complete response; SD, stable disease.

would take place. If two or more responses were seen in a group, an additional 20 patients would be accrued to that group. If at least five RECIST responses were seen in a group of 41 patients, this would be considered a positive result. Based on these numbers, there would be a $\geq .90$ probability of a positive result if the true response rate was $\geq 20\%$ and a $\geq .95$ probability of a negative result if the true response rate was $\leq 5\%$. Group C was designed to enroll 20 patients to obtain an initial estimate of the CI for response rate to therapy. Three patients with chordoma were initially enrolled in group A before the opening of group C. None of these patients achieved an objective response. For the purposes of this report, all patients with chordoma are included in group C for clarity of assessing sunitinib in this limited number of patients with this disease.

RESULTS

Patient Characteristics

A total of 53 patients were enrolled from April 2007 to March 2008. One patient was enrolled but deemed ineligible before starting sunitinib due to a history of bleeding diathesis. A total of 52 patients received at least one dose of sunitinib and therefore were included in the toxicity evaluation. Four patients were unassessable for response: one patient was found to be ineligible after receiving study drug due to lack of measureable disease, one patient experienced a grade 4 toxicity (thrombocytopenia and gastrointestinal bleed) unrelated to study drug before restaging and withdrew from study, and two patients chose to pursue alternative lines of treatment before tumor reassessment. Therefore, 48 patients were assessable for response: 21 patients in group A, 21 patients in group B, and six patients in group C. Further enrollment to group C was stopped due to slow accrual to this cohort. Patient characteristics at baseline are outlined in Table 1.

Activity: RECIST Response

RECIST response data for assessable patients are summarized in Table 2. Of the 48 patients assessable for response, there were 11 patients (22%) who remained with stable disease or PR by RECIST for at least 16 weeks, and seven patients (14%) who met this criteria at 24 weeks. The one confirmed PR was in a heavily pretreated patient in group B with DSRCT who remained on treatment for 56 weeks. Durable disease control was seen a variety of other histologies as presented in Table 3: two patients with solitary fibrous tumor, four patients with chordoma, and one patient each with synovial sarcoma, liposarcoma, alveolar soft parts sarcoma, and malignant giant cell tumor of bone achieved disease control for at least 16 weeks (range, 17 to 70+ weeks). Progression-free survival curves for the entire patient population, and for each subgroup are shown in Figure 1.

FDG-PET/CT

FDG-PET/CT results obtained after one cycle of sunitinib are available for 21 patients (86 lesions). Based on the EORTC criteria, metabolic PR was observed in 40 lesions, metabolic SD in 40, and metabolic PD in six (Table 4). Overall metabolic PR was seen in 10 patients, metabolic SD in 11 patients, and no patient showed metabolic PD (Table 4 and Fig 2). Of note, four patients who had reached metabolic PR were actually characterized as anatomic PD by RECIST and taken off therapy. Since medical decisions were based on

Table 3. Disposition of Patients Remaining on Treatment for at Least 16 Weeks

Group	Tumor Type	Best Response	Time on Study (weeks)	Reason Off Study
B	DSRCT	PR	56	Progressive disease
A	Hemangiopericytoma	SD	58+	Still on study
A	Hemangiopericytoma	SD	24	Chose to pursue surgery instead
B	Giant cell tumor of bone	SD	68+	Still on study
B	ASPS	SD	67+	Still on study
B	Liposarcoma	SD	28	Progressive disease
B	Synovial sarcoma	SD	16	Withdrew consent to pursue therapy with another agent
C	Spinal chordoma	SD	70+	Still on study
C	Sacral chordoma	SD	51	Progressive disease
C	Clival chordoma	SD	18	Chose to pursue surgery instead
C	Clival chordoma	SD	17	No longer able to visit study site

NOTE. N = 48 patients assessable for response.
Abbreviations: DSRCT, desmoplastic round cell tumor; PR, partial response; SD, stable disease; ASPS, alveolar soft parts.

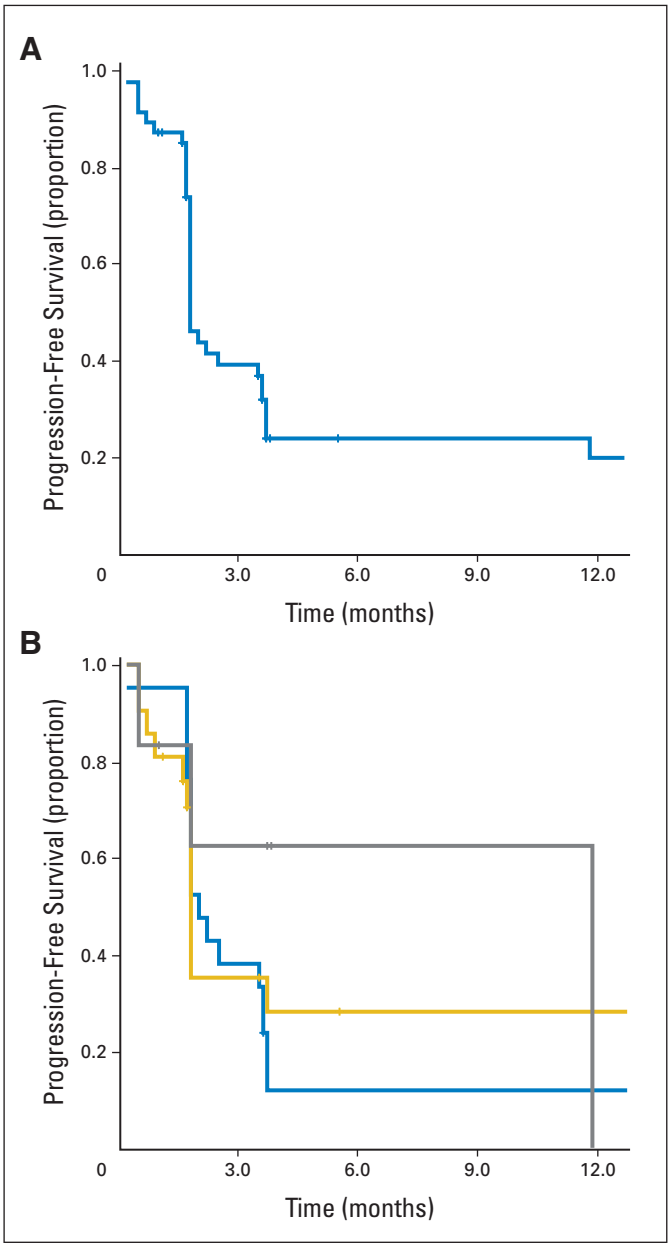

Fig 1. Progression free survival (PFS). (A) PFS for the entire patient population, median 1.8 months. (B) PFS per group; group A, blue; group B, gold; and group C, gray.

anatomic criteria, the discrepancy between the anatomic PD and metabolic PR group of patients could not, therefore, be further assessed. While there were no patients with metabolic PD based on the summed SUVmax, two patients had two lesions with PD and two patients had one lesion with PD suggesting that there was heterogeneous response/progression in four of 11 patients. It is interesting to note that four of five patients who remained on drug for more than 100 days showed metabolic PR while all of them (five of five) remained with SD by anatomic criteria.

Safety

The majority of toxicities encountered on study were grade 1 or 2, with the most common nonhematologic AEs being fatigue (50%), diarrhea (42%), elevated thyroid-stimulating hormone (TSH) levels (31%), nausea (27%), hand-foot skin reaction (21%), mucositis (21%), and hypertension (19%). Grade 3 or 4 adverse events felt related to sunitninb therapy were less common and are presented in Table 5. There were no grade 4 toxicities attributed to sunitinib. Of not, there was a grade 4 gastrointestinal hemorrhage which was felt to be related to the patient's underlying disease. Three patients experienced asymptomatic (grades 1 and 2) reductions in left ventricular systolic function while on study. Hypertension was also observed but was typically mild with one instance of grade 3 severity.

Hematologic laboratory abnormalities similarly were mild (generally grades 1 and 2) with the most common being thrombocytopenia (25%), neutropenia (11%), anemia (8%), and other leukopenias (12%). Grade 3 thrombocytopenia (8%), anemia (6%), and other leukopenias (2%) related to sunitinib were less common, and there were no related grade 4 hematologic abnormalities.

Table 4. [^{18}F]-Fluorodeoxyglucose Positron Emission Tomography Metabolic Response Assessment Results by European Organisation for Research and Treatment of Cancer Criteria

Metabolic Response	Lesions		Patients	
	No.	%	No.	%
PR	40/86	47	10/21	48
SD	40/86	47	11/21	52
PD	6/86	7	0/21	0

Abbreviations: PR, partial response; SD, stable disease; PD, progressive disease.

DISCUSSION

Treatment of sarcomas poses a particular challenge given the heterogeneous biologic underpinnings and variability in responses to therapy. Recently, however, efforts have been made to categorize and understand sarcoma subtypes by their molecular characteristics. This has led to therapeutic success in such sarcomas as GISTs and dermatofibrosarcoma protuberans that have particular molecular alterations in tyrosine kinase pathways making them susceptible to treatment with the tyrosine kinase inhibition.[3,4] Gene expression profiling has revealed that a number of sarcomas have high levels of expression of tyrosine kinases or receptor tyrosine kinases, making them potential targets for therapy with tyrosine kinase inhibitors.[14,15]

Sarcoma subtypes included in group A included vascular connective tissue neoplasms, including angiosarcomas, intimal sarcomas, and hemangiopericytomas (solitary fibrous tumor). These tumors may arise from endothelial cells, suggesting that inhibition of proangiogenic growth factors including VEGFR1, VEGFR2, VEGFR3, PDGFRα, and PDGFRβ may be relevant to their growth.[16,17] Desmoid and DFSP tumors had been observed clinically to respond to tyrosine kinase inhibition in prior trials and case reports, making these tumors reasonable targets as well, likely through inhibition of PDGFR.[4,5,18-21] Finally, prior studies had suggested activity of multitargeted tyrosine kinase inhibitors in leiomyosarcomas, although no clear mechanism for this could be discerned.[22] Group C, comprised by chordomas, was evaluated due to tumor expression of PDGFRβ and prior evidence of clinical activity of tyrosine kinase activity.[23,24]

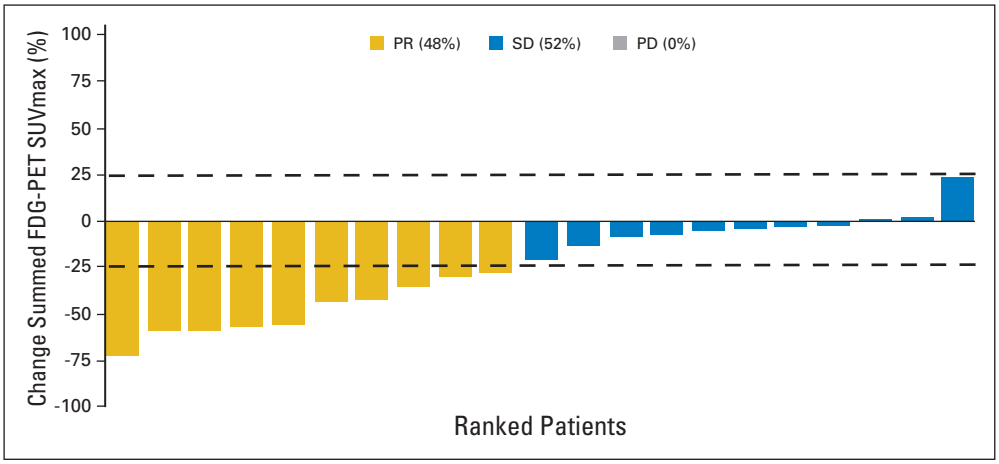

Fig 2. Waterfall plot showing overall metabolic response of patients by European Organisation for Research and Treatment of Cancer criteria. PR, partial response; SD, stable disease; PD, progressive disease; FDG-PET, [^{18}F]-fluorodeoxyglucose positron emission tomography; SUV max, maximum standardized uptake value.

Unlike some subtypes in groups A and C, none of the subtypes included in group B had demonstrated any clear responses to tyrosine kinase inhibitors in previous research.

Actual tumor responses to sunitinib differed somewhat from what was expected. Group A included two instances of SD. Importantly, this disease control was seen in two patients with solitary fibrous tumors (hemangiopericytoma). Solitary fibrous tumor is known to express PDGFR and VEGFR, and inhibition of these targets, may be the basis for the responses seen in our study. This observation builds on two prior case reports of solitary fibrous tumors responding to sunitinib.[25,26] While responses to imatinib (likely via PDGFRβ) have previously been seen in desmoid tumors,[5] no response was seen in the one desmoid tumor studied who received sunitinib, although this very limited number of patients precludes the ability to make a generalization about the potential activity of sunitinib in desmoid tumors. There was no meaningful activity seen in leiomyosarcomas enrolled on this study based on RECIST response.

The one PR seen in the trial was in a patient from group B with desmoplastic small round cell tumor. These tumors are characterized by the *EWS-WT1* fusion oncogene that results in activated PDGFRα and PDGFRβ.[27] Although this molecular signature was known, no clinical evidence of efficacy of tyrosine kinase inhibitors had been previously reported, making the current experience with sunitinib intriguing and worthy of further evaluation as a single agent or in combination with other agents.

Chordomas have demonstrated evidence of activated PDGFR and response to receptor tyrosine kinase inhibition in prior studies.[23,24] In this study, 44% of chordoma patients achieved SD for at

Table 5. Nonhematologic Adverse Events and Hematologic Laboratory Abnormalities Related to Sunitinib

Adverse Event or Laboratory Abnormality (N = 52)	Grade							
	1 and 2		3		4		All	
	No.	%	No.	%	No.	%	No.	%
Nonhematologic adverse events								
Fatigue	26	50	1	2	0	0	27	52
Diarrhea	22	42	3	6	0	0	25	48
Elevated thyroid stimulating hormone levels	16	31	0	0	0	0	16	31
Nausea	14	27	0	0	0	0	14	27
Hand-foot	11	21	4	8	0	0	15	29
Mucositis	11	21	5	10	0	0	12	23
Hypertension	10	19	1	2	0	0	11	21
Transaminitis	8	15	3	6	0	0	11	21
Hyperbilirubinemia	8	15	0	0	0	0	8	15
Taste alteration	7	13	0	0	0	0	7	13
Hypophosphatemia	1	2	1	2	0	0	2	4
Dizziness	0	0	1	2	0	0	1	2
Febrile neutropenia	0	0	1	2	0	0	1	2
Lower GI bleed	0	0	1	2	0	0	1	2
Seizure	0	0	1	2	0	0	1	2
Hematologic laboratory abnormalities								
Thrombocytopenia	13	25	4	8	0	0	17	33
Neutropenia	11	21	2	4	0	0	13	25
Anemia	5	10	3	6	0	0	8	13

NOTE. Includes adverse events occurring in ≥ 10% of patients and all grade 3 and 4 toxicities believed to be related to sunitinib.

least 16 weeks (range, 17 to 70+weeks). In addition, although formal tumor density was not a predefined end point in this study, qualitative decreases in tumor density were observed. This is a characteristic seen repeatedly with tumor responses to VEGF-directed therapy across tumors including other types of sarcomas as well as renal cell and hepatocellular carcinomas.[16,28,29]

A broad comparison of our results using sunitinib to other studies evaluating multitargeted TKIs in soft tissue sarcomas suggests both similarities and differences in the spectrum of activity for various TKIs in soft tissue sarcomas. For example, sorefanib and pazopanib appear to have induced some degree of stability in leiomyosarcoma and numerous objective responses in synovial sarcoma, something we did not see with sunitinib.[38,39] Alternatively, responses to solitary fibrous tumor were seen with both sunitinib and sorafenib.[40] Comparisons across other sarcoma subtypes is limited, due to the small number of patients enrolled, however, although all three agents have overlapping anti VEGFR, KIT, and PDGFR activity, the binding properties of each agent may vary, and the relevant targets in these diseases is still not well understood. Interestingly, none of these agents seems to have significant activity in adipocytic sarcomas.

It is possible that sunitinib efficacy may be underestimated when local evaluation of anatomic response is performed using changes in tumor size according to RECIST, as was done in this study. Tumor density measured with contrast-enhanced CT and changes in glycolytic metabolism measured with FDG-PET may be better markers of clinical response, as has been shown other molecular-targeted drugs, such as imatinib.[30-33] In our study, nearly half of patients experienced a metabolic PR by FDG-PET within 2 weeks of therapy. Although early metabolic response did not appear to correlate with RECIST-defined response, the response by FDG-PET is encouraging in this patient population and supported by the fact that patients with anatomic SD and longer progression-free survival (> 100 days on drug) also had a FDG-PET metabolic response (four metabolic PR, one metabolic SD).

Toxicities observed among patients in this study are consistent with other published experiences with sunitinib, with fatigue, diarrhea, stomatitis, and hypertension as commonly seen adverse effects.[34] Heart failure associated with sunitinib has been clearly documented, as have alterations in thyroid function.[35-37]

Evaluation of a novel agent in sarcomas inherently presents a number of challenges. Sarcomas are an uncommon and pathologically diverse group of diseases. This study design was able to explore the activity of sunitinib in a number of histologic subtypes. There was not, however, sufficient statistical power to draw a definite conclusion regarding its efficacy for a specific tumor type. Suggestions of activity were observed in alveolar soft parts sarcoma, chordoma, and liposarcoma with stable disease for at least 24 weeks, though the significance of this may be confounded by the indolent natural history of these diseases. The benefit seen in solitary fibrous tumor, giant cell tumor of bone, chordoma, and DSRCT suggest that further evaluation of sunitinib in these sarcoma subtypes may be warranted.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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